Chemical Agents in Neoplastic Diseases

An Evaluation of Chemotherapeutic Substances for Clinical Management

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• The rapid appearance of many new chemical substances which possess some antineoplastic effects has created a complex problem for the practicing physician. These agents which have shown promise in man and lower animals are grouped according to their modes of action. Each substance is discussed thoroughly with regard to its structure, activity, and influence upon the neoplasms of man. Key references are cited, and the practical value of each chemical agent is defined. The proper methods of administration of the compounds recommended for use are carefully described. In addition a section on agents whose therapeutic value has been disproven is also included.

THE THREE BASIC AIMS of chemotherapeutic agents for neoplastic diseases are to cure, to arrest, and to palliate.[7] No chemotherapeutic agent to date has been found to cure any neoplastic disease. The cure of cancer today rests with surgical or roentgen therapy. Therefore, the agents to be discussed are either arrestive or palliative. It must also be emphasized that a given agent may arrest specific neoplasms and yet be only palliative or even totally ineffective for others. Similarly, agents ineffective when given intravenously may temporarily arrest some tumors when used topically, intra-arterially or by other modes of administration. The point of attack upon the cancer cell has many approaches and the possibilities of favorably altering these avenues of entrance into the intrinsic mechanism of neoplastic cells may materially enhance the action of substances which are currently ineffective.

The number of chemical agents which have shown some activity against neoplastic diseases has increased considerably in the past ten years. Few of these agents have had extensive clinical trial. Studies of many in animal experimentation have only recently been completed and the clinical experience is encouraging but certainly not conclusive. Of all the compounds listed, nitrogen mustard (HN_2), colchicine, urethane, arsenic, the diamidines, antimony and the endocrines are readily available. These and the remaining substances are under active employment. These latter agents must remain in the investigative stage until the evidence gathered in patients can be thoroughly evaluated for toxicity, effectiveness and possible late, untoward reactions.

The agents have been grouped relative to their alleged mode of action or origin to assist physicians in gaining some insight for proper selection of the substances in the management of some neoplastic diseases (Table 1).

I. RADIOMIMETIC AGENTS

1. *Nitrogen mustards: Beta-chloroethyl amines (HN_2 and HN_3).* Over 600 congeners of methyl-bis (Beta-cholorethyl) amine (HN_2) have been prepared[119, 22, 80, 81] but none have been shown to possess any significant therapeutic advantage over HN_2 or HN_3.[81, 135, 158] In many institutions, HN_2 is administered in doses of 0.1 mg. per kilogram of body weight daily for three or four consecutive days in strict adherence to the early recommendations concerning its use.[119, 22] The administration of the total dose per kilogram of body weight in one single dose is equally effective, simpler and less traumatic to the patient since the nausea and vomiting following the HN_2 occurs only once and not three or four times as with the divided dose schedule.[14]

The material is best given into the stream of a rapid infusion of isotonic saline solution (Figure 1). The infusion should be started with a large bore needle (No. 18) to ensure a constant full stream of saline solution runnning rapidly when the HN_2 is injected into the stream through the rubber tubing attached to the needle. The HN_2 should be dissolved in isotonic saline solution, 10 cc. per bottle (10 mg.), reaspirated into a Luer-Lok® syringe and administered as rapidly as possible after solution. A No. 18 needle permits rapid mixing, but the injection into the saline infusion stream is best accomplished with a No. 25 or No. 26 needle. This technique minimizes or prevents thrombosis of the vein because the HN_2 is well diluted by the large volume of the saline infusion and does not irritate the vein.

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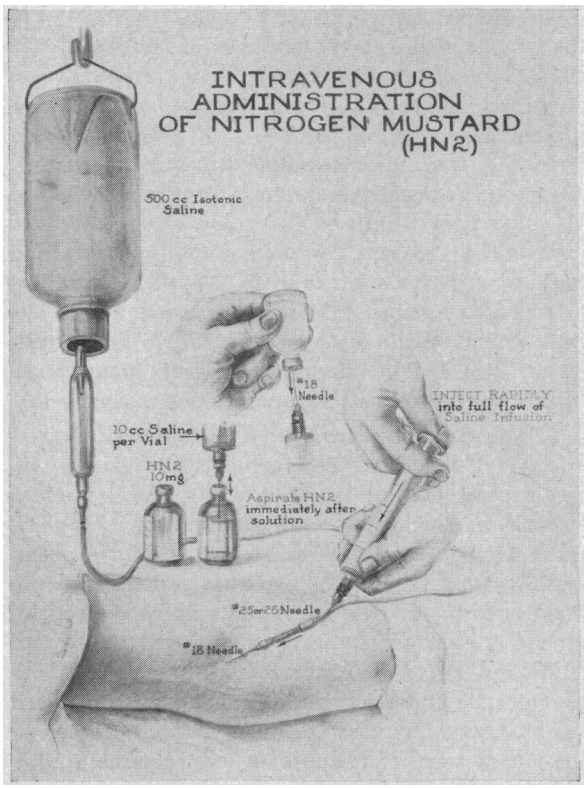

Figure 1.—A method of safe administration of agents which otherwise might cause venous thromboses. No. 18 needles are employed for rapid infusion of saline solution and for solution and transfer of the chemical. The smaller needle (No. 25 or No. 26) prevents too rapid administration.

The toxic effects of HN_2 are mainly those of depression of the hematopoietic tissues.[79] In patients with normal hematopoiesis, doses of 0.3 mg. per kilogram of body weight may be given at four- to six-week intervals for four to six months since the dearth of leukocytes is greatest 10 to 14 days following HN_2 and usually the number of leukocytes returns to normal within 20 to 25 days after administration.[14] In patients with impaired hematopoietic function, the intervals at which HN_2 may be readministered must be determined by frequent hematological study. It is advisable to count the leukocytes and platelets three times each week and the erythrocytes weekly until the count returns to normal. Occasional patients have pronounced sensitivity to HN_2 characterized by extreme nausea and retching, generalized erythema, and exhaustion. A generalized maculopapular eruption similar to that described by Zanes[170] has also been observed. A distinct conditioned reflex develops in some patients so that nausea and retching will occur *prior* to administration if the HN_2 is prepared in the presence of the patient.

Although the leukocyte count frequently falls to and below 1,000 per cu. mm. of blood following the repeated administration of HN_2 intravenously, the original fears of fulminating infections during the agranulocytic period have not been realized. The thrombocytopenia, however, is of more serious consequence. Patients may be permitted to be ambulatory with the leukocyte count fluctuating between 1,500 and 4,000 cu. mm. provided they are carefully

TABLE 1.—*Agents Under Investigation for the Treatment of Neoplastic Diseases*

I. RADIOMIMETIC AGENTS
1. Nitrogen mustards: Beta-chloroethyl amines (HN_2 and HN_3)
2. Triethylene melamine: Trisethylene-imino-s-triazine (TEM)
3. R-48: Beta-naphthyldi-2-chloroethyl amine
4. Hemi-sulfur mustard: 2-chloro-2′-hydroxydiethyl sulfide (HSM)

II. MITOTIC INHIBITORS
1. Colchicine
2. Podophyllin and Podophyllotoxin
3. Peltatins
4. Urethane: ethyl carbamate
5. Arsenic: Potassium arsenite (Fowler's solution)

III. SUBSTANCES TOXIC TO CELLS
1. GT-41: 1,4,dimethane sulfonoxy butane
2. Diamidines: Stilbamidine and Pentamidine
3. Alloxan: Mesoxyl urea
4. Antimony

IV. ANTIMETABOLITES
1. Folic acid antagonists: 4-amino pteroyl-glutamic and aspartic acids
2. Adenine antagonist: 2,6-diaminopurine
3. Guanine antagonist: 8-azaguanine
4. Pyridoxine antagonist: desoxypyridoxine
5. Para-amino-benzoic acid (PABA)
6. Riboflavin inhibitor: galacto-riboflavin and iso-riboflavin
7. Melanin antagonist: Mono-benzyl ether of hydroquinone

V. ENDOCRINE SUBSTANCES
1. Androgens: Testosterone propionate, methyltestosterone and methylandrostenediol (MAD)
2. Estrogens: Stilbestrol, estradiol and related compounds
3. Progesterone
4. Corticotropin (ACTH)
5. Cortisone: 17-hydroxy-11-dehydrocorticosterone (Compound E)
6. Para-hydroxy-propiophenone

VI. BIOLOGIC AND BACTERIAL PRODUCTS
1. Shear's polysaccharide
2. Lymphokentric and myelokentric acids
3. Rabies vaccine

VII. AGENTS OF RECENT INTEREST WHOSE EFFECTIVENESS HAS NOT BEEN SUBSTANTIATED TO DATE
1. Krebiozen
2. ACS—Antireticular cytotoxic serum
3. K-R: Klyueva-Roskin vaccine
4. Chymotrypsin

and frequently observed, although antibiotics may be deliberately withheld until definitely indicated. If bleeding occurs, strenuous antihemorrhagic measures should be initiated.

A patient with a single initial node of Hodgkin's disease without evidence of any other involvement is best treated by wide surgical excision followed by intensive irradiation of the area if there is any doubt concerning total excision. Where more than a single area is involved, x-ray therapy to the local sites in combination with HN_2 for the systemic involvement is advisable. Like x-ray therapy, nitrogen mustard will lose its original beneficial effect after repeated employment. On the other hand, the initial administrations of nitrogen mustard occasionally may be disappointing and subsequent doses prove effective, so that it is not wise to forsake HN_2 after the initial courses until it is certain that the patient will not respond to this agent. If a patient with a diagnosis of Hodgkin's disease does not respond to either x-ray or HN_2, a careful reevaluation of the biopsy material should be undertaken to substantiate the diagnosis, particularly to exclude a malignant thymoma.[96] Nitrogen mustard is a useful adjunct to radiotherapy of Hodgkin's disease and particularly serviceable after irradiation has lost its effectiveness. While this therapy does not prolong life over conventional x-ray treatment, it reduces the requirements for radiation, the asymptomatic periods are longer and the patient is more easily controlled.[46]

Nitrogen mustard is effective for shorter periods in lymphosarcoma (lymphoblastic or lymphocytic types) than in Hodgkin's disease. The clasmatocytic or primitive cell lymphosarcoma (reticulum cell sarcoma) often does not respond to nitrogen mustard but in an occasional case there may be pronounced benefit from this agent.

Patients with widespread mycosis fungoides are often benefited by HN_2 for periods of one to five months but eventually the favorable response can no longer be repeated. While the intravenous administration of HN_2 will favorably influence the course of patients with lymphomata, it has failed completely in the treatment of other neoplasms except possibly for some transient effects in bronchogenic carcinoma.[135, 14] Investigations upon the blood supply of tumors have revealed that many neoplasms possess an increased arterial blood supply,[10] increased capillary permeability[12] and a characteristic vascular pattern upon arteriography.[13] The intra-arterial administration of HN_2 leading directly to localized mycosis fungoides lesions of the extremities results in prompt clearing of the involved areas. The administration of HN_2 intra-arterially directed to the tumor site results in higher concentrations of HN_2 at the tumor site than can be attained safely by the intravenous route[8] and has caused considerable dissolution of many types of neoplasms unrelated to the lymphoid series although in no instance were the lesions completely eradicated. Temporary improvement for months has been observed in approximately 30 per cent of patients with widespread, far-advanced, visceral metastases involving the liver, kidney and lung that were so treated.[8, 9] Klopp and his associates[88] infused HN_2 intra-arterially into superficially located carcinomas of the head and neck over periods of four to ten days and pronounced regression of the neoplasms was noted. The intra-arterial route of therapy is still in the investigative stage but this approach presents many possibilities for a direct attack upon tumor masses.

2. *Triethylene melamine: Trisethylene-imino-s-triazine (TEM).* This compound is the result of investigations to find less distressing and less toxic substances which exert mustard-like activity.[124] Triethylene melamine, abbreviated to TEM, is chemically related to HN_2 by its transformation in the body to form ethylene-imine rings which are considered the pharmacologically active group of both TEM and HN_2.[118] TEM can be administered both parenterally and orally without immediate untoward reaction, and in most instances without emesis although nausea and anorexia are common complaints.[169, 82, 136] The intravenous dosage is about 0.05 mg. per kilogram of body weight, the total single dosage never to exceed 5 mg. Doses in excess of 0.25 mg. per kilogram of body weight intravenously are lethal in man.[136] Orally the dose is 0.1 to 0.3 mg. per kilogram of body weight, and the material is dispensed in 5 mg. tablets. The total oral daily dose should not exceed one tablet (5 mg.): if larger doses are contemplated, three to four days should elapse between the doses.

The major toxic effects of TEM are essentially similar to those of the nitrogen mustards, the major component of which is the depression of the hematopoietic system, resulting in leukopenia, thrombocytopenia and, less often, anemia. As multiple doses of TEM are cumulative, too frequent or excessive administration of the material may result in toxic effect beyond that generally anticipated.[136] Leukocyte and platelet counts three times each week and erythrocyte counts weekly should be done to follow the patient properly with this agent and to estimate when therapy can be reinstituted.

The major advantage of TEM over HN_2 is the oral route of administration and the decreased incidence of nausea and vomiting. Although TEM may produce pronounced changes in the course of patients with Hodgkin's disease, it is neither as effective nor as predictable as HN_2 in this disease.[82,136,114] In patients with lymphosarcoma and chronic lymphatic leukemia, the effectiveness of TEM more nearly approaches that of HN_2. TEM is also of value

in the treatment of chronic myelocytic leukemia and mycosis fungoides.[82, 136, 114, 168, 138, 126] It is of little aid in the arrest or palliation of carcinomas.[168, 126]

3. *R-48: Beta-naphthyldi-2-chloroethylamine.* This compound, which has been studied extensively in Great Britain,[56, 103, 19] acts similarly to the nitrogen mustards. R-48 is inactivated by light and for adults is administered orally in divided doses for a total of 300 to 400 mg. daily, never to exceed 600 mg. per day. The dose for children is 100 mg. per day. A maintenance dose is apparently difficult to establish. Seventeen patients treated with R-48 have been reported.[103] Five patients had Hodgkin's disease, two reticulum cell sarcoma, two acute leukemia, three chronic myeloid leukemia, four chronic lymphatic leukemia, and one polycythemia vera. Nausea or gastric disturbances were slight or absent although vomiting did occur in two patients. Hemorrhagic cystitis with dysuria was noted on two occasions.[103] Protracted administration of R-48 might inhibit ovulation or endometrial proliferation. There were two instances of pronounced leukopenia in 11 courses of treatment in eight patients. Lymphocytopenia and thrombocytopenia occur. R-48 also acts on primitive, granulocytic forms in the marrow. R-48 will cause transient responses in the lymphomata with less nausea and vomiting than with HN_2. The best effects were observed in chronic lymphatic leukemia. Hematopoietic depression is the major toxic complication, as with HN_2, HN_3 and TEM.

4. *Hemi-sulfur mustard: 2-chloro-2'-hydroxydiethyl sulfide (HSM).* This compound is reported to be one-thirteenth as toxic as HN_2.[131] Intravenous administration in man was followed by nausea, vomiting, malaise and weakness. Ten patients of 31 treated with HSM were benefited.[131] Eight of 13 patients with ascites presumably from peritoneal carcinomatosis showed a striking decrease in ascites formation for two to six months. There were no hematological changes with doses from 100 to 400 mg. repeated three or four times at one-day to four-day intervals. Thromboses or phlebitis of the vein occurred with each injection until the material was given through plastic tubing passed proximally into the vena cava from a peripheral site. Intention tremors of hands and fingers, noted in nine patients, subsided in one to two days after the last dose. Convulsions occurred in two patients.

II. MITOTIC INHIBITORS

1. *Colchicine.* Neoplastic cells can be altered and destroyed by colchicine but the doses required to produce such changes induce toxic effects[112, 128, 94] which approach lethality. The regression of tumors following colchicine is probably due in large part to hemorrhages within the capillary blood supply[98] but many further studies in man must be completed to evaluate colchicine properly.

2. *Podophyllin and podophyllotoxin.* Podophyllin, a plant extract composed of resins, has been used most effectively to remove condylomata acuminata by topical application. Within a few hours after podophyllin is painted upon the verrucous excrescences, degenerative changes in the area can be seen and within a few days the lesion will shrivel and disappear. Colchicine also acts topically like podophyllin upon condyloma acuminata.[150] MacCardle and Perrault,[99] investigating the action of podophyllin and its active principle, podophyllotoxin,[149,150] observed a neurological disturbance in fowl characterized chiefly by unsteady gait. Histological examination showed destruction of the cerebellar Purkinje cells. Parenteral administration of these substances in patients did not influence neoplastic disease favorably.[130]

3. *Peltatins:* Leiter, Downing, Hartwell and Shear[93] further isolated a group of compounds from crude podophyllin and then synthesized various related congeners whose action simulated that of podophyllotoxin. One group of related compounds, termed *peltatins*, was investigated by Greenspan, Leiter and Shear[53] in mice transplanted with various neoplastic diseases. These compounds produced specific alterations in tumor cells which resembled those obtained with colchicine. The chemical formulae of podophyllotoxin and the peltatins are quite similar. Later 45 patients with various neoplastic diseases received alpha-peltatin, 0.1 to 0.5 mg. per kilogram of body weight intravenously. Although a few instances of transient regressions of lesions were observed, they occurred at dose levels which produced toxic reactions.[52]

4. *Urethane: Ethyl carbamate.* Interest in the carbamic esters was revived by the studies of Templeman and Sexton[155] who confirmed the growth-suppressive findings of Lefevre.[92] Soon thereafter Haddow and Sexton[57] demonstrated that ethyl carbamate (urethane) produced profound histological changes in tumors in mice and rats. Urethane is preferably given with meals in enteric-coated tablets, in capsules or in liquid form. Parenteral administration remains experimental and cannot be recommended.

Urethane is of value in the treatment of chronic myelogenous leukemia with peripheral leukocytosis.[6, 71, 115] Doses of 1 to 4 gm. per day will result in a fall in the peripheral leukocyte count in two to four weeks, usually associated with generalized clinical improvement in about one-third of the patients so treated. A decrease in hepatosplenomegaly and lymphadenopathy are often observed although the decrease is less than that which occurs with x-radia-

tion or P^{32} therapy. The erythrocyte level usually remains unchanged although occasionally it will fall or, less often, rise. The platelet count is usually maintained.[6] Urethane may serve as a useful therapeutic agent in this disease in the absence of x-ray P^{32} or GT-41.

Rundles reported benefit in nine of 16 patients with widespread multiple myeloma who received one or more courses of treatments.[95, 127] The course of treatment was for eight to ten weeks in total doses of 120 to 290 grams in two months and repeated during an 18-month period for a total amount of 1,850 grams. Within two to four weeks after therapy was begun, skeletal pain and fever subsided, the hematological condition improved and the content of abnormal proteins in the serum became less or disappeared. Recalcification of widespread skeletal lesions has been observed in four to six months.[127] Accessible areas of skeletal involvement are best treated by x-radiation.

The exact mode of action of urethane upon neoplastic tissues is obscure but it has been reported that it is rapidly and completely metabolized within 24 hours and that the rate of breakdown is slower in tumor-bearing mice than in normal mice.[106] Urethane is a hematopoietic depressant and protracted daily administration can result in marrow hypoplasia with persistent leukopenia, thrombocytopenia and anemia. Gastric irritation with nausea and vomiting are common complaints with oral administration, but these conditions disappear promptly upon decrease in dosage or cessation of therapy. Blood studies at least twice each week are necessary for the proper control of therapy with this agent. The depression of the bone marrow elements is relieved slowly after cessation of therapy.

5. *Arsenic: Potassium arsenite (Fowler's solution).* Arsenic is employed most effectively as potassium arsenite (Fowler's solution) in doses of 15 to 30 drops per day in the treatment of chronic myelogenous leukemia.[42] Potassium arsenite inhibits mitosis at metaphase in a characteristic fashion similar to that of urethane but different from that of HN_2.[5] Since protracted arsenical therapy is hematopoietically depressant and cumulative, frequent hematological examination is necessary when this agent is employed.

III. SUBSTANCES TOXIC TO CELLS

1. *GT-41: 1, 4, dimethane sulfonoxy butane.* Following the demonstration that some sulfonic acid esters possessed radiomimetic activity,[18, 58, 161] Galton[44] reported the effectiveness of 1,4,dimethane sulfonoxy butane (GT-41) in myeloid leukemia. Three patients with chronic myelogenous leukemia were treated with 1,4,dimethane sulfonoxy butane, 8 mg. per day for four weeks for a total dosage of 200 to 250 mg. In all cases there was rapid clinical improvement during which the appetite was regained as well as strength, the enlarged spleen regressed in size, the hemoglobin rose and there was an accelerated decrease in primitive granulocytic leukocytes with an increase in mature forms in the peripheral blood.[44] GT-41 has been shown to reduce total leukocyte count, almost exclusively at the expense of the immature granulocytic forms. Accordingly, its clinical value lies in the hypercellular forms of chronic myelocytic leukemia. In the more fulminant forms of myelocytic leukemia with a preponderance of early immature granulocytes, the anemia and thrombocytopenia usually become progressively more severe despite a decrease in the leukocyte count. The effective dosage is 25 mg. daily for three to six days, and the decrease in leukocytes occurs within the next seven to ten days. Excessive dosage results in hypoplasia of the marrow with thrombocytopenia, anemia and leukopenia which may be fatal. Maintenance doses are difficult to establish.

2. *Diamidines: Stilbamidine and Pentamidine.* Stilbamidine® and Pentamidine® were introduced by Snapper[141] as therapeutic agents for multiple myeloma. Many interesting reactions of the diamidines with cellular nucleic acids were observed.[142] Clinical trials even in massive doses afforded temporary relief of bone pain in about half of the patients; the ultimate course of the disease was unaltered.[48, 59] The recommended course of parenteral therapy is 100 to 150 mg. every other day for 15 doses, repeated after a two-week rest interval, for a total of 4 to 6 grams over a period of four to five months. Rapid intravenous administration may produce hypotension, dyspnea, paresthesias and signs of impending shock. Electrocardiograms may show pronounced changes suggestive of myocardial ischemia if the injection is too rapid.[15]

Approximately 25 to 50 per cent of patients receiving intramuscular or intravenous Stilbamidine have paresthesias, and hypesthesias along the fifth cranial nerve distribution during or shortly after protracted treatment. These facial paresthesias have persisted permanently in some patients.[48] Pentamidine is claimed to cause facial neuropathologic change and other toxic manifestations less often than does Stilbamidine. Since x-irradiation and urethane have shown much more favorable effects, the use of these diamidines for multiple myeloma is limited. Diamidines are not considered preferable to conventional analgesics for the relief of pain and they are more likely to cause untoward side reactions.

3. *Alloxan: Mesoxyl urea.* Brunschwig and Allen[21] originally treated a patient with an islet cell tumor of the pancreas by intravenous administration of

alloxan.[34] Beneficial results with alleviation of frequent hypoglycemic episodes in that one case led to trials on other neoplasms and conditions with varying equivocal success.[21, 153] Other investigators[40] using alloxan intravenously in carcinoma of the pancreas did not observe favorable changes.

4. *Antimony:* Antimony has been used previously to influence the course of neoplastic diseases[3] and while the changes produced have not been dramatic, some alteration in the hematologic disorders have been reported.[97] More recently Rubinstein[125] employed Neostibosan® in the treatment of multiple myeloma with equivocal results.

The mode of action of antimony as a growth-suppressive is obscure but evidence indicates that it is closely related to that of arsenic.[51]

IV. ANTIMETABOLITES

The biological function of many essential metabolic substances may be antagonized by other compounds with closely related chemical structures. This antagonism between essential metabolites and their structural analogs may be utilized to interrupt specific cellular functions. In this manner sulfanilamide blocks the utilization of para-amino-benzoic acid by some bacteria, and scurvy can be produced in guinea pigs by the administration of gluco-ascorbic acid. Similar alterations in normal cellular enzyme metabolism may be produced by other vitamin analogs.[167]

1. *Folic acid antagonists.* Of the metabolic antagonists which have undergone animal or clinical trial, the 4-amino derivatives of folic acid have shown the most pronounced effects upon neoplastic diseases.[39] Three closely related substances, 4-amino pteroyl-glutamic acid (Aminopterin®), 4-amino N^{10} methyl pteroyl-glutamic acid (A-methopterin®) and 4-amino pteroyl-aspartic acid (Amino-an-fol®), have received extensive trial in the leukemias in the past four years. Aminopterin and A-methopterin have produced pronounced alterations in the hematopoietic tissues with temporary remissions in 20 to 30 per cent of children with lymphatic leukemia.[36, 37, 145, 157] The severe toxicity so frequently encountered with small to moderate amounts of these antagonists often necessitates discontinuance of the therapy.

The folic-acid antagonists are usually administered orally or intramuscularly in doses determined specifically for each patient. The usual dose of Aminopterin for children is 0.5 to 1.0 mg. daily; for A-methopterin it is 2 to 5 mg. daily in children and 5 to 10 mg. in adults parenterally or by mouth. For amino-an-fol it is 30 to 75 mg. per day intramuscularly—the smaller doses for children, the larger for adults. Adults tolerate Aminopterin less well than children on the basis of body weight. The dosage usually is gradually reduced and continued until manifestation of toxicity appears. Clinical improvement usually appears during the initial phases of the bone marrow depression. Macrocytosis, megaloblastosis and multilobulation of the neutrophils have been observed with small doses during Aminopterin therapy of leukemia in man and animals[76, 156] and have been attributed to the production of folic acid deficiency.[78] Hematopoietic depression of the blood and marrow elements may progress to complete aplasia if the dosage is not discontinued or promptly reduced. If therapy is protracted, other more systemic toxic signs soon appear—ulcerations of the entire gastrointestinal mucous membranes from the mouth to the anus, associated with diarrhea, hemorrhage, weakness and anorexia. Alopecia and skin eruptions of many varieties may occur during therapy, but these conditions are ameliorated when use of the drug is discontinued.[24]

The acute signs and symptoms of toxic reaction to therapy with folic acid antagonists may be partly ameliorated by the administration of folic acid, or folinic acid (citrovorum factor).[143, 154, 166] Large doses of these substances will completely override the antagonist. In children the course of leukemia is most often rapid, and approximately 90 per cent of cases are of the lymphatic type.[11] The natural history of untreated lymphatic leukemia in children is characterized by a variable course of two to 16 months with an average of 5.6 months. Supportive therapy with blood and antibiotics will increase the average survival to 8.9 months. This is about equal to the mean life span of children treated with hormones or antagonists in addition to support with blood and antibiotics.[11]

In a four-year period, 311 patients with acute leukemia were treated with folic acid antagonists by the Farber group.[38] Of these, 243 were treated for three weeks or longer. Approximately two-thirds of the 243 are reported to have responded favorably to these compounds. The mean survival of the 311 patients was calculated to be nine months. However, of the patients treated for three weeks or longer, 58 or 18.6 per cent survived more than 12 months; 39 or 12.1 per cent survived more than 15 months; 26 or 8.3 per cent more than 18 months, and seven or 2.2 per cent more than 29 months. Of the seven who lived more than 29 months, five were alive at the time of report. With the exception of the five living children, the remainder of 243 patients treated for three weeks or longer sooner or later reached a point at which the folic acid antagonists were no longer effective. The citrovorum factor had no value in the prevention or treatment of toxicity which could not be equalled by careful administration of the antagonists alone.

Farber and co-workers reemphasized that the remissions were temporary, that the compounds were

toxic, that there was no evidence that would justify the term "cure" of acute leukemia in children, and that value of these compounds is still limited to research. However, it must be considered that definite prolongation of life occurred in some members of the group treated. Both intermittent and continuous administration of the antagonists have been employed and in some instances the addition of corticotropin (ACTH) or cortisone to the regimen has been of great aid as concerns the comfort of the patients, and perhaps in further prolongation of life.[69, 120]

2. *Adenine antagonist: 2,6-diaminopurine.* Burchenal and co-workers[23, 25] studied an adenine antagonist, 2,6-diaminopurine, and found this compound to prolong the life of leukemic mice. Clinically, however, the drug was inconsistent in action and ineffective when employed in patients with acute leukemia.

3. *Guanine antagonist: 8-azaguanine.* Similarly 8-azaguanine (Guanazolo®), a guanine antagonist, was ineffective in clinical trials although it inhibited a mammary carcinoma EO771 in mice.[4, 86] This compound when administered orally to patients with various neoplastic diseases in doses of 50 to 100 mg. per day for 10 to 14 consecutive days caused diarrhea and marked erythematous excoriations of the skin.[4]

Combined treatment with Guanazolo plus Aminopterin, Guanazolo plus alpha-peltatin, and Aminopterin plus alpha-peltatin had an additive inhibitory action upon a transplantable mouse leukemia (lymphoma 1210), without extra toxicity.[49, 50] Combinations of 8-azaguanine with an antiriboflavin compound or with stilbestrol caused tumor inhibition in mammary adenocarcinoma of mice.[43, 132]

4. *Pyridoxine antagonist: Desoxypyridoxine.* In mice and rats, inhibition of growth of transplantable tumors while the animals were receiving pyridoxine-deficient diets was observed.[87] The addition of desoxypyridoxine to the deficient diet slowed the growth of a transplanted lymphosarcoma in mice.[146] Clinical trials in acute leukemia and lymphosarcoma, however, were without favorable effect.[47]

5. *Para-amino-benzoic acid (PABA).* Zarafonetis and co-workers[171] found that leukopenia occurred following protracted administration of large doses of para-amino-benzoic acid and that it was relieved promptly upon cessation of therapy.[172] High content of the drug in the blood can be maintained with doses of 2 to 4 grams every two hours. Profound and consistent but transient hematopoietic effects were observed in chronic myelogenous leukemia more frequently than in chronic lymphatic leukemia.

6. *Riboflavin inhibitors: Galacto-riboflavin and Iso-riboflavin.* Galacto-riboflavin and Iso-riboflavin will suppress the growth of some animal tumors on riboflavin-deficient diets both in vitro and in vivo.[35, 147]

7. *Melanin antagonist:* Mono-benzyl ether of *hydroquinone.* Oliver and co-workers[111] reported the depigmenting properties of a compound while studying the cause of skin changes in workers from a commercial rubber manufacturing plant. The causative material, mono-benzyl ether of hydroquinone, interferes with the normal melanin metabolism. Hence it was employed in investigations to influence malignant melanomas. Kelly and co-workers[85] treated nine patients with malignant melanoma with large oral doses of this substance. The patients were closely observed and chemical and cytologic studies of the blood and examination of biopsy material were carried out frequently. No significant or consistent favorable alteration of the natural course of the disease was observed.

V. ENDOCRINE SUBSTANCES

Hormonal therapy of advanced mammary cancer is arrestive or palliative but not curative under any conditions.[54, 107, 163] Only five types of neoplastic disease are altered by hormonal therapy—lesions of the breast, prostate, uterus, lymphatic and hematopoietic systems. Roentgen therapy is most advantageous for arrest or palliation when metastases are localized and accessible yet beyond the scope of surgical treatment.[45] Hormonal therapy is preferable for widespread soft tissue, visceral or osseous metastases.

Approximately 25 per cent of patients with advanced neoplastic involvement from carcinoma of the breast will benefit objectively from therapy with estrogenic or androgenic hormones.[30, 107] Extensive clinical experience has been attained with two androgens, testosterone propionate and methyltestosterone, and with six preparations of estrogens, diethylstilbestrol, ethinyl estradiol, estradiol dipropionate, dienestrol, dimethyl ether of diethylstilbestrol and Premarin.® Postmenopausal women respond much better to estrogens than premenopausal women, and the best results are obtained in patients who are more than five years postmenopausal. The functional state of the ovaries apparently has little effect on the response to testosterone propionate. In the premenopausal and menopausal patients, estrogens and androgens are about equally effective in soft tissue lesions resulting from carcinoma of the breast, but in postmenopausal patients estrogens are superior to testosterone propionate. Occasionally acceleration of the disease occurs during hormonal therapy, most frequently in the menopausal or premenopausal patients receiving estrogens. Therefore, castration (if not contraindicated) and androgens are the treat-

TABLE 2.—*Steroid Hormones of Value in the Treatment of Advanced Mammary Cancer*

	Route	Dose schedule preferred: Mg.	Daily	Weekly	Minimal total dose
ANDROGENS:					
Testosterone propionate	Intramuscular	50-100		3	3 gm/3 mo.
	Buccalet	40- 60	1		3-5 gm/3 mo.
Methyltestosterone	Oral	200	1		30 gm/6 mo.
Methylandrostenediol	Intramuscular	100-200		3	4-7 gm/3 mo.
ESTROGENS:					
Diethylstilbestrol	Oral	15	1		2-4 gm/3-6 mo.
Ethinyl estradiol	Oral	3	1		200 mg/3-6 mo.
Estradiol dipropionate	Intramuscular	5	2		200 mg/3-6 mo.
Dienestrol	Oral	15	1		4 gm/3-6 mo.
Dimethyl ether of diethylstilbestrol	Oral	30	1		4 gm/3-6 mo.
Premarin	Oral	30	1		4 gm/3-6 mo.
TACE (tri-para-anisyl chloroethylene)	Oral	24	1		Investigative stage: to be determined

ments of choice for soft tissue lesions in the premenopausal patient. Testosterone propionate is more effective than estrogens in relieving subjective bone pain although there is little difference, objectively, between the two steroids with respect to recalcification of the osseous lesions.

1. *Androgens: Testosterone propionate, methyltestosterone and methylandrostenediol (MAD).* Testosterone propionate, 50 mg. three times each week, intramuscularly, is as effective as the previously recommended dosage of 100 mg. three times each week. Daily, frequent dosage orally or by buccal absorption may be employed as an adjunct to intramuscular administration but the equivalent dosage must be absorbed, and this is usually more expensive by the oral than by the parenteral route.[30, 107] Pellet implantation permits uniform absorption of androgens or estrogens[16, 137] and in adequate amounts will often suffice for two to three months. Hormonal therapy should be continued until definite progression of the disease resumes. Cessation of therapy may then cause another regression; and regression may also occur if a change is made to another hormone. The response to the hormones is temporary. Each eventually becomes ineffective. Some investigators feel, therefore, that the hormones should be administered intermittently, preferably cyclically, and that furthermore they should be employed sparingly to avoid premature exhaustion of the therapeutic armamentarium. On the other hand other authorities feel the hormones should be continued as long as response is favorable.

Combined androgen and estrogen therapy in patients with advanced mammary cancer is at present under trial but conclusions cannot yet be drawn.

Recently, Homburger and co-workers[73] reported favorably on the effects of methylandrostenediol, an androgen said to exert the characteristic anabolic activity of testosterone without the masculinizing accompaniments.

Kasdon and co-workers[83] reported subjective improvement in 30 of 40 patients with advanced mammary cancer treated with methylandrostenediol (MAD) administered orally, subcutaneously and by pellet implantation. In nine of the 30 there was objective evidence of improvement. Hypercalcemia, the only major side effect observed, occurred in three patients with extensive osteolytic metastases. Segaloff and his associates[129] reported similar although not so encouraging observations in 24 cases. Only two of the patients, both with soft tissue lesions, had objective regression of lesions after intramuscular administration of 300 to 700 mg. of MAD per week. There was no beneficial effect on metastases in any patient in the series.

The dosage of this androgen is approximately twice that of testosterone propionate. There has been less clinical experience with methylandrostenediol than with the older testosterone preparations, but results of recent clinical investigations with this nonvirilizing androgen are encouraging.

2. *Estrogens.* The first six estrogens listed in Table 2 are considered to exert similar activity when given in equivalent dosage. Frequently, however, some preparations are better tolerated than others. Also, a change from the oral to the parenteral route of administration may significantly ameliorate the undesirable side effects. The fact that patients with metastatic mammary cancer respond similarly to either estrogens or androgens suggests a common metabolic utilization of these compounds.

More recently a new substance, Tri-para-anisylchloroethylene (TACE), has been reported as a potent estrogen without the undesirable feminizing side effects. Its value in the treatment of advanced prostatic cancer has been suggested[140, 152] but more clinical confirmation is needed before TACE can be recommended.

Patients with advanced carcinoma of the prostate can be benefited by the administration of estrogens.[60, 74, 109] In a study of 100 consecutive cases of

carcinoma of the prostate, Harrison and Poutasse[60] found that the most effective hormonal treatment of carcinoma of the prostate was orchiectomy combined with estrogenic therapy. Seventy per cent of patients with extensive carcinoma of the prostate had symptomatic and objective improvement with this form of therapy.

All known effective measures should be instituted as soon as possible. It is desirable to reduce the androgen predominance, and there is much controversy as to whether castration, or estrogen administration or both are the preferred courses of action. In general it is felt that orchiectomy followed by prolonged oral administration of 5 to 10 mg. daily of stilbestrol or an equivalent estrogen is most effective. Since the psychological barrier of orchiectomy often is difficult to overcome, many patients are treated with estrogens alone, often with good results. The estrogens may also be administered intramuscularly, or pellets may be implanted. Approximately 75 per cent of patients so treated show subjective and often objective improvement as judged by subsidence of pain, return of appetite, gain in weight and strength, decrease in size and hardness of the prostate, relief of urinary obstruction and roentgenographic evidence of disappearance of metastases to bones. Although the regressions are temporary, there is now evidence that definite prolongation of life has been achieved.

The toxic complications with estrogens—edema, hypercalcemia, menorrhagia and metrorrhagia—are related particularly to large doses given over long periods. At least eleven instances of carcinoma of the breast have occurred in men treated with estrogens for two or more years for carcinoma of the prostate, although the association has been contested.[26] Castrodale, Bierbaum, Helvig and MacBryde[27] noted pronounced hematological and hepatic changes following prolonged administration of estradiol and stilbestrol in dogs, characterized primarily by thrombopenia with fatal hemorrhages.

Frequently nausea and vomiting occur during estrogen therapy, and although these reactions may abate after one to two weeks of therapy it is often necessary to discontinue treatment because of them. Reducing the dosage, substituting other estrogens or changing to parenteral administration may alleviate gastrointestinal distress.

The toxicity of androgens is evident after protracted administration and large dosage. In women, masculinizing and other changes appear within a few weeks—changes such as hirsutism, hoarseness, increased firmness of the musculature, increased libido, amenorrhea, water retention and hypercalcemia.[30] Upon cessation of therapy these conditions gradually subside. A salt-poor diet will often prevent water retention.

3. *Progesterone.* Large doses of progesterone (250 mg. daily) intramuscularly are reported by Hertz[67] to be associated with a decrease in size, vascularity and friability of lesions of carcinoma of the cervix. The changes are not sufficient, however, to recommend progesterone as a therapeutic agent in carcinoma of the cervix at this time.

4. *Corticotropin (ACTH).* The pituitary adrenocorticotropic hormone is available in single sterile ampules of 25 mg. The dosage varies widely depending upon the desired goal. Intramuscular doses of 50 to 200 mg. per day in two or three divided doses are most commonly employed.[121, 159] Intravenous administration of corticotropin (20 mg. daily) is comparable to intramuscular administration of five to ten times that amount and is therefore more economical.[122] Slow infusion increases the adrenal cortical response to a given dose of the hormone. The side effects are analogous to those that occur when corticotropin or cortisone is administered by other routes.

5. *Cortisone: 17-hydroxy-11-dehydrocorticosterone (Compound E).* Cortisone is the name coined by Kendall to identify 17-hydroxy-11-dehydrocorticosterone, or "Kendall's Compound E."[102] Cortisone is considered a growth-suppressive.[35, 62, 143] In some cases of neoplastic diseases in which this material was used there were definite although mostly subjective, slight and transient effects.[66, 75, 116] The intramuscular dose ranges from 25 to 100 mg. per day, usually given once or twice a day. Oral administration is equally effective in identical doses if taken daily in three to four equally divided doses.[160] Corticotropin and cortisone probably reduce the tissue reaction to neoplasms with little or no favorable effect on the cancerous process itself.[159]

The effects and complications of corticotropin and cortisone are identical as far as can be ascertained today and are ascribable directly or otherwise to their metabolic or endocrine functions.[144, 159] It should be emphasized that corticotropin causes adrenal cortical hypertrophy and cortisone is associated with cortical atrophy. The unfavorable effects of corticotropin and cortisone occur with prolonged administration of large doses and are identical with the symptoms of hypercorticoidism (Cushing's syndrome)[1, 66, 144] which include impairment of carbohydrate tolerance, weakness and wasting of muscle, osteoporosis, striation of the skin, bruising tendency, rounding of the facial contours, acne, hirsutism, alkalosis, loss of gonadal activity, psychoses and hypertension.

Cortisone and corticotropin have been observed to produce striking changes in hematological dyscrasias.[159, 165] Favorable responses occur initially in about 50 per cent of patients with acute lymphatic leukemia, can seldom be repeated in the same patient

with repeated courses of therapy, and, as with other hormonal substances, loss of tolerance rapidly appears after the first or second course of therapy.

To attain therapeutic results in the lymphomas and leukemias the dosage often must be forced until at least some part of the Cushing syndrome appears. Most of this syndrome will regress quickly but often not completely following discontinuance of the therapy. The appetite which becomes voracious during corticotropin or cortisone administration will subside promptly upon cessation of treatment. Prolonged metabolic changes such as the development of diabetes mellitus, malignant or benign hypertension, peptic ulceration, cardiac failure and permanent psychotic changes have not been reported.[70] Corticotropin and cortisone may depress the natural immunological processes in infections, resulting in enhancement of susceptibility and increased severity.[84]

6. *Para-hydroxy-priopiophenone.* This material has been reported by Buu-Hoi to exert pituitary-like effects and in clinical trials it is stated to have brought about temporary remissions in the course of various neoplastic diseases.[41, 117] Preliminary trials with this material (H365) in this country have not given any indications to date that would confirm the findings of the French investigators.

VI. BIOLOGIC AND BACTERIAL PRODUCTS

1. *Shear's polysaccharide.* The occasional regression of neoplastic lesions following infections and the administration of Coley's toxin to patients with advanced neoplastic diseases stimulated interest in similar biologic products.[108] Shear and co-workers purified preparations from Bacillus prodigiosus (Serratia marcescens) and obtained a group of polysaccharides[133] containing phospholipid and nitrogen fractions which decreased with greater purification. The material was administered intravenously in doses of 5 to 15 micrograms. Within 45 to 60 minutes fever, leukocytosis and hypotension occurred, with shock and occasionally death.[20, 72, 110] Temporary tumor regression was observed occasionally, associated with transient clinical improvement. Creech and co-workers employed newer polysaccharide preparations with similar results.[32] The substance is pyrogenic in man and produces hemorrhages within the tumors of both mice and man. The effect of the polysaccharides is primarily upon the vascular supply, related to systemic toxicity, and not directly upon the tumor cells.[2]

2. *Lymphokentric and myelokentric acids.* In 1939, Miller, Wearn and Heinle[105] reported the isolation of crude substances from the urine of leukemic patients which stimulated myelopoiesis and lymphopoiesis in animals. They named these substances lymphokentric and myelokentric acids. Eight patients with lymphoblastic leukemia were treated with myelokentric acid with equivocal changes and a suggestion of partial remissions.[104] Swan and Zelman observed similar phenomena in a patient with acute lymphoblastic leukemia treated with myelokentric acid.[151]

3. *Rabies vaccine.* Two of twelve patients with malignant melanoma treated with rabies vaccine had some regression of metastatic nodules without microscopic cellular alterations.[113] A later report[68] indicated that eight of thirty patients had definite regression of metastases and the authors felt that the development of new metastases was also retarded.

VII. OTHER AGENTS OF RECENT INTEREST

1. *Krebiozen.* Krebiozen is a substance reported to be derived from the blood of horses which have been inoculated with a stimulating material the nature of which has not been disclosed as yet.[77] By another process (also undisclosed) approximately 1.0 mg. of a white powder is obtained which is then diluted in distilled water for intramuscular administration. Although it has been specifically stated that Krebiozen is not antireticular cytotoxic serum (ACS) the approach is quite similar.[17] Extensive studies on neoplasms in mice, rats and dogs treated with Krebiozen by the Chicago group elicited no objective evidence of any effect upon these tumors.

Initial investigations upon 22 patients with various neoplasms were stated to show decrease in size of a lymphosarcomatous lesion in the breast of a 52-year-old woman and some decrease in nodes of a patient with Hodgkin's disease. Changes in the remaining 20 patients[77] were within the natural variation of neoplastic illnesses.

In studies in other laboratories on the use of Krebiozen in 100 patients with a wide variety of neoplastic diseases, no significant alteration in the course of the disease was noted in 98 cases.[31] In the other two patients transient changes occurred which were considered significant but within the natural variation of the specific disease. It must be concluded that the substance termed Krebiozen has not to date been shown capable of favorably influencing the neoplastic diseases studied, that the original claims concerning Krebiozen are without substantiation[31, 123, 164] and that the material cannot be recommended for use as a tumor chemotherapeutic agent at this time.

2. *Antireticular cytotoxic serum (ACS).* Bogomolets and his associates[17, 101] obtained a material from the blood of horses following the injection of human spleen and bone marrow tissue which, they reported, caused disappearance of metastases in lymph nodes and prolongation of life in inoperable cancer. The

substance was termed antireticular cytotoxic serum (abbreviated to ACS) and was proposed as an adjunct in the therapy of cancer to prolong useful life by causing regression of metastases, alleviation of pain and increase of appetite.[17] In neither clinical nor animal investigations in this country have such specific effects been observed upon benign or malignant tumors in mice, rats or man.[33, 63, 64, 65, 139]

3. *K-R: Klyueva-Roskin vaccine.* This water soluble, heat-stable endotoxin derived from Trypanosoma Cruzi was reported to cause regressions in both animal and human neoplasms.[89] Although a report by Malisoff[100] contained favorable implications, other more intensive studies by Cohen, Borsook and Dubnoff[28] in vitro and by Hauschka in vivo[61] in mice did not confirm the original claims. No reports upon this material have appeared recently.

4. *Chymotrypsin.* Independent clinical investigations by two groups[134,162] employing chymotrypsin[91] have failed to confirm the original claims made by Krebs and co-workers.[55, 90] Serious reactions were observed in four of ten patients treated over a protracted period, one of whom almost died following anaphylactoid reaction to an injection. No further authentic substantiation of the claims made for this material have appeared since. Chymotrypsin cannot be recommended as an effective agent for tumor chemotherapy.[29]

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REFERENCES

1. Albright, F.: Cushing's syndrome; its pathological physiology, Harvey Lectures, 38:123-186, 1943.

2. Algire, G. H., Legallais, F. Y., and Park, H. D.: Vascular reactions of normal and malignant tissues in vivo. II. The vascular reaction of normal and neoplastic tissues of mice to a Bacterial polysaccharide from Serratia marcescens (Bacillus prodigiosus) culture filtrates, J. Nat. Cancer Inst., 8:53-62, 1947.

3. Allen, F. M.: Combinations of lead, arsenic and other chemicals with experimental asphyxia of tumors, J. Lab. & Clin. Med., 26:1120-1128, 1941.

4. Armistead, G. C., Jr., Burchenal, J. H., Karnofsky, D. A., and Southam, C. M.: Preliminary studies on the clinical toxicity of 5-amino-7 hydroxy-1-v-triazolo(d) pyrimidine(guanazolo), Cancer, 2:1087-1088, 1949.

5. Bastrup-Madsen, P.: Action of nitrogen mustards and potassium arsenite on living cells in vitro, pp. 1-116, 1950. Universitets for Laget 1 Aarhus, Copenhagen, Denmark.

6. Berman, L., and Axelrod, A. R.: Effect of urethane on malignant diseases, Am. J. Clin. Path., 18:104-129, 1948.

7. Bierman, H. R.: Newer methods of treatment of leukemias and lymphomas, Calif. Med., 69:285-289, Oct. 1948.

8. Bierman, H. R., Byron, R. L., Jr., and Kelly, K. H.: Hepatic arteriography and the effect of intra-arterial chemotherapeutic agents on metastatic neoplasms of the liver, Am. J. Med., 11:625, 1951.

9. Bierman, H. R., Byron, R. L., Jr., and Kelly, K. H.: Therapy of inoperable visceral and regional metastases by intra-arterial catheterization in man, Cancer Res., 11:236, 1951.

10. Bierman, H. R., Byron, R. L., Jr., Kelly, K. H., and Grady, A.: Studies on the blood supply of tumors in man. III. Vascular patterns of the liver by hepatic arteriography in vivo, J. Natl. Cancer Inst., 12:107-117, Aug. 1951.

11. Bierman, H. R., Cohen, P., McClelland, J. N., and Shimkin, M. B.: The effect of transfusions and antibiotics upon the duration of life in children with lymphogenous leukemia, J. Pediatrics, 37:455-462, Oct. 1950.

12. Bierman, H. R., Kelly, K. H., Dod, K. S., and Byron, R. L., Jr.: Studies on the blood supply of tumors in man. I. Fluorescence of cutaneous lesions, J. Natl. Cancer Inst., 11: 877-889, April 1951.

13. Bierman, H. R., Miller, E. R., Byron, R. L., Jr., Dod, K. S., Kelly, K. H., and Black, D. H.: Intra-arterial catheterization of viscera in man, Am. J. Roentgenology & Radium Therapy, 66:555-568, Oct. 1951.

14. Bierman, H. R., Shimkin, M. B., Mettier, S. R., Weaver, J., Barry, W. C., and Wise, S. P.: Methyl-bis (Beta-Chloroethyl) amine in large doses in the treatment of neoplastic diseases, Calif. Med., 71:117-125, Aug. 1949.

15. Bierman, H. R., and Sokolow, M.: Cardiovascular effects produced by stilbamidine in patients with multiple myeloma, J. Natl. Cancer Inst., 10:279-289, Oct. 1949.

16. Bishop, P. M. F., and Folley, S. J.: Absorption of hormone implants in man, Lancet, 2:229-232, Aug. 1951.

17. Bogomolets, A. A.: Anti-reticular cytotoxic serum as means of pathogenic therapy, Am. Rev. Soviet Med., 1:101-112, 1943.

18. British Empire Cancer Campaign, Ann. Report, pp. 43, 1949: Bifunctional esters of bis-B-hydroxyethyl arylamines.

19. British Empire Cancer Campaign: Twenty-eighth Annual Report, 1950.

20. Brues, A. M., and Shear, M. J.: Chemical treatment of tumors: reactions of four patients with advanced malignant tumors to injection of polysaccharide from Serratia marcescens culture filtrate, J. Nat. Cancer Inst., 5:195-208, 1944.

21. Brunschwig, A., and Allen, J. G.: Specific injurious action of alloxan upon pancreatic islet cells and convoluted tubules of the kidney. Comparative study in the rabbit, dog and man, Cancer Research, 4:45-54, 1944.

22. Burchenal, J. H.: The newer nitrogen mustards in the treatment of leukemia, Radiology, 50:494-499, 1948.

23. Burchenal, J. H., Bendrich, A., Brown, G. B., Elion, G. B., Hitchings, G. H., Rhoads, C. P., and Stock, C. C.: Preliminary studies on the effect of 2, 6, diaminopurine on transplanted mouse leukemia, Cancer, 2:119-120, 1949.

24. Burchenal, J. H., Karnofsky, D. A., Southam, C. M., Myers, W. P. L., Craver, L. F., Dargeon, H. W., and Rhoads, C. P.: The effects of 4-amino-pteroylglutamic acid and related compounds on neoplastic disease. To be published.

25. Burchenal, J. H., Webber, L. F., Meigs, G. M., and Biedler, J. L.: A comparison of the effects of 4-amino-N^{10} methyl-pteroyl glutamic acid and 2, 6, diaminopurine upon sensitive and resistant sublines of a strain of mouse leukemia, Blood, 6:337-343, 1951.

26. Campbell, J. H., and Cummins, S. A.: Metastases, simulating mammary cancer, in prostatic carcinoma under estrogenic therapy, Cancer, 4:303-311, 1951.

27. Castrodale, D., Bierbaum, O., Helvig, E. B., and MacBryde, C. M.: Comparative studies of the effect of estradiol and stilbestrol upon the blood, liver and bone marrow, Endocrinology, 29:363-372, 1941.

28. Cohen, A. L., Borsook, H., and Dubnoff, J. W.: Effect of sporosarcina ureae preparation on tumor cells in vitro, Proc. Soc. Exper. Biol. & Med., 66:440-444, 1947.

29. Council on Pharmacy and Chemistry: Cancer and the need for facts, J.A.M.A., 139:93-98, 1949.

30. Council on Pharmacy and Chemistry: Current status of hormone therapy of advanced mammary cancer, J.A.M.A., 146:471-477, June 1951.

31. Council on Pharmacy and Chemistry: A status report on "Krebiozen," J.A.M.A., 147:864-873, Oct. 1951.

32. Creech, H. J., Hamilton, M. A., and Diller, J. C.: Comparative studies of the immunological, toxic and tumor-necrotizing properties of polysaccharides from Serratia marcescens (Bacillus prodigiosus), Cancer Res., 8:318-329, 1948.

33. Davis, W. D., Jr.: Clinical observations in patients treated with anti-reticular cytotoxic serum. Preliminary report, Am. J. Med., 3:123, 1947.

34. Dunn, J. S., Sheehan, H. L., and McLetchie, N.: Necrosis of islets of Langerhans produced experimentally, Lancet, 1:484-487, 1943.

35. Emerson, G. A., Wurtz, E., and Zanetti, M. E.: Regression of lymphosarcoma transplants following the administration of cortisone to riboflavin-deficient mice, Fed. Proc., 9:357-358, 1950.

36. Farber, S.: Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer, Blood, 4:160-167, 1949.

37. Farber, S.: Folic acid antagonists in the treatment of leukemia, Blood, 7:97-190 Supplement, Jan. 1952.

38. Farber, S., Appleton, R. E., Downing, V., Heald, F. P., King, J. P., and Toch, R.: Folic acid antagonists in the treatment of acute leukemia, lymphosarcoma and Hodgkin's disease, Proc. Second National Cancer Conference, Cincinnati, Ohio, March 1952.

39. Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., Jr., and Wolff, J. A.: Temporary remissions in acute leukemia in children produced by folic acid antagonists, 4-aminopteroyl-glutamic acid (Aminopterin), New Eng. J. Med., 238:787-793, 1948.

40. Flinn, L. B., Minnick, E., and Gay, D. M.: Alloxan in treatment of islet cell carcinoma of pancreas with liver metastases, Ann. Int. Med., 26:936-945, 1947.

41. Foreign Letters: Paraoxypropiophenone, a powerful synthetic hypophysial inhibitor, J.A.M.A., 145:341-342, Feb. 1951.

42. Forkner, C. E.: Leukemia and Allied Disorders, Macmillan Co., New York, 1938.

43. Fugmann, R. A., and Shapiro, D. M.: Combination cancer chemotherapy with 8-azaguanine and a riboflavin antagonist, Abst. Cancer Res., 12:263, 1952.

44. Galton, D. A. G.: 1, 4, Dimethanesulphonoxybutane in myeloid leukemia, British Empire Cancer Campaign Ann. Rep., 28:77-78, 1950.

45. Garland, L. H.: Roentgen and steroid hormone therapy in mammary cancer metastatic to bone, J.A.M.A., 144: 997-1004, Nov. 1950.

46. Gellhorn, A., and Collins, V. P.: A quantitative evaluation of the contribution of nitrogen mustard to the therapeutic management of Hodgkin's disease, Ann. Int. Med., 35:1250-1259, 1951.

47. Gellhorn, A., and Jones, L. O.: Pyridoxine-deficient diet and desoxypyridoxine in the therapy of lymphosarcoma and acute leukemia in man, Blood, 4:60-65, 1949.

48. Gibson, A., and Pogge, R. C.: Stilbamidine in the treatment of multiple myeloma. A summary of 194 cases, Medical Division, Merck & Co., Inc., April 1948.

49. Goldin, A., Greenspan, E. N., and Schoenbach, E. B.: Studies on synergism of several anti-neoplastic agents, Fed. Proc., 10:542, June 1951.

50. Goldin, A., Greespan, E., and Schoenbach, E. B.: Studies on the mechanism of action of chemotherapeutic agents in cancer. VI. Synergistic (additive) action of drugs on a transplantable leukemia in mice, Cancer, 5:153-160, 1952.

51. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, Macmillan Co., New York.

52. Greenspan, E. M., Colsky, J., Schoenbach, E. B., and Shear, M. J.: Preliminary observations following the administration of peltatin to patients with neoplastic disease, Cancer Research, 12:266-267, 1952.

53. Greenspan, E. M., Leiter, J., and Shear, M. J.: Effect of Alpha-peltatin, Beta-peltatin and podophyllotoxin on lymphomas and other transplanted tumors, J. Nat. Cancer Inst., 10:1295-1333, 1950.

54. Griboff, S. I.: The rationale and clinical use of steroid hormones in cancer, A.M.A. Archives of Internal Medicine, 89:635-685, 812-852, 1952.

55. Gurchot, C., Krebs, E. T., Jr., and Krebs, E. T.: Growth of human trophoblast in eye of rabbit: its relationship to the origin of cancer, Surg., Gynec. and Obst., 84: 301-311, 1947.

56. Haddow, A., Kon, G. A., and Ross, W. C. J.: Effects upon tumors of various halo alkylarylamines, Nature, London, 162:824-825, 1948.

57. Haddow, A., and Sexton, W. A.: Influence of carbamic esters (urethanes) on experimental animal tumors, Nature, London, 157:500-503, 1946.

58. Haddow, A., and Timmis, G. M.: Bifunctional sulphonic acid esters with radiomimetic activity, Acta Union internat. contre cancer, 7:469-471, 1951.

59. Haedicke, T. A., and Greenspan, E. M.: Massive stilbamidine therapy of multiple myeloma, Am. J. Clin. Path., 19:634-638, 1949.

60. Harrison, J. H., and Poutasse, E. F.: Management of carcinoma of the prostate, Amer. J. Med., 11:55-66, 1951.

61. Hauschka, T. S., and Goodwin, M. R.: Trypanosoma cruzi endotoxin (K-R) in treatment of malignant mouse tumors, Science, 107:600-602, 1948.

62. Heilman, F. R., and Kendall, E. C.: The influence of 11-dehydro-17-hydroxycorticosterone (Compound E) on the growth of a malignant tumor in the mouse, Endocrinology, 34:416-420, 1944.

63. Heiman, J., and Meisel, D.: Anti-reticular cytotoxic serum (ACS). I. The effect of ACS on tumor growth in rats, Cancer, 2:329-334, 1949.

64. Heiman, J., and Meisel, D.: II. The effect of ACS in mice with transplanted and spontaneous mammary tumors, Cancer, 2:335-336, 1949.

65. Heiman, J., and Meisel, D.: III. Reduced incidence of spontaneous mammary cancer in R3 mice treated with ACS, Cancer, 2:337-340, 1949.

66. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions, Arch. Int. Med., 85:545-666, 1950.

67. Hertz, R., Cromer, J. K., Young, J. P., and Westfall, B. B.: Observations on the Effect of Progesterone on Carcinoma of the Cervix. Symposium on steroids in experimental and clinical practice. Edited by A. White, Blakiston Co., Philadelphia, 1951.

68. Higgins, G. K., and Pack, G. T.: Virus therapy in the treatment of tumors, Bull. Hosp. Joint Dis., 12:379-382, 1951.

69. Higgins, G. M., and Woods, K. A.: The influence of the adrenal gland on some of the changes induced in the animal organism by the folic acid analogue, aminopterin, Proc. Staff Meet. Mayo Clin., 24:533-537, Oct. 1949.

70. Himsworth, H. M.: Complications of cortisone and ACTH therapy, Lancet, 2:79, July 1951.

71. Hirschboeck, J. S., Lindert, M. C. F., Chase, J., and Calvy, T. L.: Effects of urethane in the treatment of leukemia and metastatic malignant tumors, J.A.M.A., 136:90-95, 1948.

72. Holloman, A. L.: Reactions of patients and of tumors to injection of S. marcescens polysaccharide in eight cases of malignant disease, in Approaches to Tumor Chemotherapy, pp. 273-276.

73. Homburger, F., Kasdon, S. C., and Fishman, W. H.: Methylandrostenediol: non-virilizing derivative of testosterone in metastatic cancer of breast, Proc. Soc. Exper. Biol. & Med., 74:162-164, 1950.

74. Huggins, C.: Anti-androgenic treatment of prostatic carcinoma in man, Approaches to Tumor Chemotherapy. American Assoc. Advancement Science, Washington, D. C., 379-383, 1947.

75. Ingle, D. J.: The biologic properties of cortisone; a review, Jour. Clin. Endocrinol., 10:1312-1354, Oct. 1950.

76. Isaacs, R., and Trimmer, R. W.: Blood cell changes in leukemia during aminopterin therapy, Ann. Int. Med., 35:236-239, 1951.

77. Ivy, A. C., Krasno, L., Phillips, W. F., Pick, J. F., and Grubgeld, L. E.: Krebiozen: an agent for the treatment of malignant tumors, Chicago, 1951.

78. Jukes, T. H., Franklin, A. L., and Stokestad, E. L.: Pteroylglutamic acid antagonists, Ann. N. Y. Acad. Sci., 52:1336-1341, 1950.

79. Karnofsky, D. A., Graef, I., and Smith, H. W.: Studies on the mechanism of action of the nitrogen and sulfur mustards in vivo, Am. J. Path., 24:275-292, 1948.

80. Karnofsky, D. A., Abelmann, W. H., Craver, L. F., and Burchenal, J. H.: The use of the nitrogen mustards in the palliative treatment of carcinoma with particular reference to bronchogenic carcinoma, Cancer, 1:634-656, 1948.

81. Karnofsky, D. A.: Nitrogen mustards in the treatment of neoplastic disease. In Dock, W., and Snapper, I., Eds.: Advances in Internal Medicine, Chicago Year Book Publishers, Inc., 4:1-75, 1950.

82. Karnofsky, D. A., Burchenal, J. H., Armistead, G. C., Jr., Southam, C. M., Bernstein, J. L., Craver, L. F., and Rhoads, C. P:. Triethylene melamine in the treatment of neoplastic disease, Arch. Internal Med., 87:477-516, April 1951.

83. Kasdon, S. C., Fishman, W. H., Dart, R. M., Bonner, C. A., and Homburger, F.: Methylandrostenediol in palliative treatment of breast cancer, J.A.M.A., 148:1212-1216, April 1952.

84. Kass, E. H., and Finland, M.: Role of adrenal steroids in infection and immunity, New Eng. J. Med., 244:464-470, 1951.

85. Kelly, K. H., Bierman, H. R., and Shimkin, M. B.: Negative effects of oral monobenzyl ether of hydroquinone in malignant melanoma in man, Proc. Soc. Exp. Biol. & Med., 79:589-590, April 1952.

86. Kidder, G. W., Dewey, V. C., Parks, R. E., Jr., and Woodside, C. L.: Purine metabolism in tetrahymena and its relation to malignant cells in mice, Science, 109:511-514, 1949.

87. Kline, B. E., Rusch, H. P., Baumann, C. A., and Lavik, P. S.: Effect of pyridoxine on tumor growth, Cancer Research, 3:825-829, 1943.

88. Klopp, C. T., Alford, C., Bateman, J., Berry, G. N., and Winship, T.: Fractionated intra-arterial cancer chemotherapy with methyl-Bis-amine hydrochloride; a preliminary report, Ann. Surg., 132:811-832, 1950.

89. Kluyeva, N. G.: Paths of cancer biotherapy, Am. Rev. Soviet Med., 4:408-414, 1947.

90. Krebs, E. T., Krebs, E. T., Jr., and Gurchot, C.: Skeletal changes associated with the use of crystalline chymotrypsin in an apparently radioresistant growth, M. Rec., 160: 479, Aug. 1947.

91. Kunitz, M., and Northrup, J. H., Jr.: Crystalline chymotrypsin and chymotrypsinogen. I. Isolation, crystallization and general properties of a new proteolytic enzyme and its precursor, J. Gen. Physiol., 18:433-458, 1935.

92. Lefevre, J.: Similitude des actions cytologiques exercees par le phenylurethane et la colchicine sur des plantules vegetales, Compt. rend. Acad. d. Sc., 208:301-304, 1939.

93. Leiter, J., Downing, V., Hartwell, J. L., and Shear, M. J.: Damage induced in sarcoma 37 with podophyllin, podophyllotoxin, alpha-peltatin, beta-peltatin, and quercetin, J. Nat. Cancer Inst., 10:1273-1293, 1950.

94. Levine, M., and Silver, G. B.: Mitotic response to colchicine in human cancer, Proc. Soc. Exp. Biol. & Med., 65:54-60, 1947.

95. Loge, J. P., and Rundles, R. W.: Urethane (ethyl carbamate) therapy in multiple myeloma, Blood, 4:201-216, March 1949.

96. Lowenhaupt, E., and Brown, R.: Carcinoma of the thymus of granulomatous type, Cancer, 4:1193-1209, 1951.

97. Lucia, S. P., and Brown, J. W.: Hematopoietic reactions to antimonyl antimony, Proc. Soc. Exper. Biol. & Med., 31:426, 1934.

98. Ludford, R. J.: Colchicine in experimental chemotherapy of cancer, J. Nat. Cancer Inst., 6:89-101, 1945.

99. MacCardle, R. C., and Perrault, A.: Degeneration of cerebellar Purkinje cells in tumor-bearing animals after subcutaneous injection of podophyllin, Acta de l'Union Internat. Contre le Cancer, 6:539-541, 1949.

100. Malisoff, W. M.: The action of the endotoxin of trypanosoma cruzi (K-R) on malignant mouse tumors, Science, 106:591-594, Dec. 1947.

101. Marchuk, P. D.: A method of preparing and preserving of anti-reticular cytotoxic serum, Am. Rev. Soc. Med., 1:113-123, 1943.

102. Mason, H. L., Meyers, C. S., and Kendall, E. C.: The chemistry of crystalline substances isolated from the suprarenal gland, J. Biol. Chem., 114:613-631, 1936.

103. Matthews, W. B.: A trial of beta-naphthyldi-2-chloroethylamine (R48) in leukemia, Hodgkin's disease, and allied diseases, Lancet, 1:896-899, 1950.

104. Miller, F. R., Herbut, P. A., and Jones, H. W.: Treatment of lymphoblastic leukemia with crude myelokentric acid, Blood, 2:15-39, 1947.

105. Miller, F. R., Wearn, J. T., and Heinle, R. W.: Proliferation of myeloid and lymphoid cells induced by extracts of urine from leukemic patients, Proc. Soc. Exper. Biol. & Med., 41:479-480, 1939.

106. Mitchell, J. H., Hutchison, O. S., Skipper, H. E., and Bryan, C. E.: Carbamates in the chemotherapy of leukemia. VII. The rate of catabolism of urethane in normal and neoplastic mice, J. Biol. Chem., 180:675-680, 1949.

107. Nathanson, I. T., and Kelley, R. M.: Hormone treatment of cancer, N. Eng. Jour. Med., 246:135-145, 180-189, 1952.

108. Nauts, H. C., and Coley, B. L.: A Review of Treatment of Malignant Tumors by Coley Bacterial Toxins. In Approaches to Tumor Chemotherapy, edited by F. R. Moulton, pp. 217-235, Washington, D. C., American Association for the Advancement of Science, 1947.

109. Nesbit, R. M., and Baum, W. C.: Endocrine control of prostatic carcinoma, J.A.M.A., 143:1317-1320, 1950.

110. Oakey, R.: Reactions of patients to injection of S. marcescens polysaccharide in nine further cases of malignant disease. In Approaches to Tumor Chemotherapy, pp. 227.

111. Oliver, E. A., Schwartz, L., and Warren, L. H.: Occupational leukoderma, Arch. Derm. & Syph., 42:993-1014, 1940.

112. Oughterson, A. W., Tennant, R., Jr., and Hirshfield, J. W.: Effect of colchicine on human tumors, Proc. Soc. Exp. Biol. & Med., 36:661-664, 1937.

113. Pack, G. T.: Note on the experimental use of rabies vaccine for melanomatosis, Arch. Dermat., 62:694-695, Nov. 1950.

114. Paterson, E., and Boland, J.: Trisethylene imino-s-triazine in human malignant disease: A preliminary trial, Brit. J. Cancer, 5:28-37, 1951.

115. Paterson, E., ApThomas, I., Haddow, A., and Watkinson, J. M.: Leukemia treated with urethane compared with deep x-ray therapy, Lancet, 1:677-682, 1946.

116. Pearson, O. H., Eliel, L. P., and Talbot, T. R.: The use of ACTH and cortisone in neoplastic disease, Bull. New York Acad. Med., 26:235-239, 1950.

117. Perrault, M.: Etat actuel du H365 Para-oxy-Propiophenone Frenateur Hypophysaire de Synthese, Presse Med., 58:1010-1013, 1950.

118. Philips, F. A., and Thiersch, J. B.: The nitrogen mustard-like actions of 2, 4, 6-tris(ethylenimino)-s-triazine and other bis(ethylenimines), T. Pharm. & Exp. Therap., 100:398-407, 1950.

119. Philips, F. S.: Recent contributions to the pharmacology of bis(2-haloethyl) amines and sulfides, Pharm. Rev., 2:281-323, 1950.

120. Pierce, M.: Treatment of 37 cases of acute leukemia in children with ACTH, Proc. Second Nat'l Cancer Congress, Lymphoma Leukemia Panel, March 1952.

121. Proc. First Clin. ACTH Conf., Mote, J. R., Ed. The Blakiston Co., Philadelphia and Toronto, 1950.

122. Renold, A. E., Forsham, P. H., Maisterrena, T., and Thorn, G. W.: Intravenously administered ACTH, N. E. Jour. Med., 244:796-798, 1951.

123. Rhoads, C. P.: Comments and communication, Krebiozen, Science, 114:285, Sept. 1951.

124. Rose, F. L., Henry, J. A., and Walpole, A. L.: New cytotoxic agents with tumor-inhibitory activity, Nature, London, 165:993-996, 1950.

125. Rubinstein, M. A.: Use of antimony in multiple myeloma, Blood, 4:1068-1072, Sept. 1949.

126. Rundles, R. W., and Barton, W. B.: Triethylene melamine in the treatment of neoplastic disease, Blood, 7:483-507, May 1952.

127. Rundles, R. W., and Reeves, R. J.: Multiple myeloma. II. Variability of roentgen appearance and effect of urethane therapy on skeletal disease, Am. J. Roentgenol., 64:799-809, 1950.

128. Seed, L., Slaughter, D. P., and Limarzi, L. R.: Effect of colchicine on human carcinoma, Surgery, 7:696-709, 1940.

129. Segaloff, A., Gordon, D., Horwitt, B. N., Schlosser, J. V., and Murison, P. J.: Hormonal therapy in cancer of the breast. II. Effect of methylandrostenediol on clinical course and hormonal excretion, Cancer, 5:271-274, March 1952.

130. Seligman, A.: Personal communication.

131. Seligman, A. M., Rutenberg, A. M., Persky, L., and Friedman, O. M.: Effect of 2-chloro-2'hydroxydiethyl sulfide (hemi sulfur mustard) on carcinomatosis with ascites, Cancer, 5:354-363, March 1952.

132. Shapiro, D. M.: Combination cancer chemotherapy with 8-azaguanine and sex hormones on a mouse breast cancer, Abst. Cancer Res., 12:295-296, 1952.

133. Shear, M. J., and Turner, F. C.: Chemical treatment of tumors. V. Isolation of the hemorrhage-producing fraction from Serratia marcescens (Bacillus prodigiosus) culture filtrates, J. Nat. Cancer Inst., 4:81-97, 1943.

134. Shimkin, M. B., and Bierman, H. R.: Chymotrypsin in cancer, Proc. Soc. Exp. Biol. & Med., 71:250-252, June 1949.

135. Shimkin, M. B., and Bierman, H. R.: Experimental chemotherapy of neoplastic diseases, Radiology, 53:518-529, Oct. 1949.

136. Shimkin, M. B., Bierman, H. R., Kelly, K. H., Lowenhaupt, E., and Furst, A.: Trisethylene-imino-s-triazine (triethylene melamine or TEM) in the treatment of neoplastic diseases, Calif. Med., 75:26-34, July 1951.

137. Shimkin, M. B., Lorenz, E., Wyman, R., and Norton, S. G.: Absorption of subcutaneously implanted hormone pellets, Endocrinology, 35:283-295, 1944.

138. Silverberg, J. H., and Dameshek, W.: Use of triethylene melamine in treatment of leukemia and leukosarcoma, J.A.M.A., 148:1015-1021, March 1952.

139. Skapier, J.: Therapeutic use of anti-reticular cytotoxic serum (ACS) in Hodgkin's disease, Cancer Research, 7:369-371, 1947.

140. Smith, P. G., Rush, T. W., and Evans, A. T.: Preliminary report on the clinical use of TACE (chlorotrianisene) in treatment of prostatic carcinoma, Jour. Urol., 65: 886-889, May 1951.

141. Snapper, I.: On influence of stilbamidine on multiple myeloma, J. Mt. Sinai Hosp., 13:119-127, 1946.

142. Snapper, I., Mirsky, A. E., Ris, H., Schneid, B., and Rosenthal, M.: Development of inclusion bodies containing ribose nucleic acid in myeloma cells after injections of stilbamidine: determination of stilbamidine in myeloma tissue, Blood, 2:311-322, 1947.

143. Snell, E. E., and Cravens, W. W.: Reversal of aminopterin inhibition in the chick embryo with desoxyribosides, Proc. Soc. Exper. Biol. & Med., 74:87-91, 1950.

144. Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Observations in the physiologic effects of cortisone and ACTH in man, Arch. Int. Med., 85: 199-258, 1950.

145. Stickney, J. M., Mills, S. D., Hagedorn, A. B., and Cooper, T.: The treatment of acute leukemia with folic acid antagonists, Proc. Staff Meet. Mayo Clin., 24:525-533, Oct. 1949.

146. Stoerk, H. C.: The regression of lymphosarcoma implants in pyridoxine-deficient mice, J. Biol. Chem., 171:437-438, Nov. 1947.

147. Stoerk, H. C., and Emerson, G. A.: Complete regression of lymphosarcoma implants following temporary reduction of riboflavin-deficiency in mice, Proc. Soc. Exp. Biol. & Med., 70:703-704, 1949.

148. Straus, B., Jacobson, A. S., Berson, J. H., Bernstein, I. C., Fadem, R. S., and Yalow, R. S.: The effect of cortisone in Hodgkin's disease, Am. J. Med., 12:170-189, 1952.

149. Sullivan, B. J., and Wechsler, H. L.: Cytological effects of podophyllin, Science, 105:433, 1947.

150. Sullivan, M., and Blanchard, D.: Podophyllotoxin, Bull. Johns Hopkins Hospital, 81:65-67, 1947.

151. Swan, M. M., and Zelman, S.: Myelokentric acid in the treatment of acute lymphoblastic leukemia, Ann. Int. Med., 438:442, 1950.

152. Tace Symposium One, Vol. 1, No. 7, Spring 1952, Cincinnati, Ohio, Wm. S. Merrell Co., Jan. 1952. In press.

153. Talbot, N. B., Crawford, J. D., and Bailey, C. C.: Use of mesoxalyurea (Alloxan) in treatment of an infant with convulsions due to idiopathic hypoglycemia, Pediatrics, 1:337-345, 1948.

154. Taylor, A., and Carmichael, N.: Folic acid analogs

and the growth of embryo and tumor tissue, Cancer Research, 11:519-522, July 1951.

155. Templeman, W. A., and Sexton, W. A.: Effect of some arylcarbamic esters and related compounds upon cereals and other plant species, Nature, London, 156:630, 1945.

156. Thiersch, J. B.: Bone marrow changes in man after treatment with aminopterin, A-methopterin, and amino-anfol with special reference to megaloblastosis and tumor remission, Cancer, 2:877-883, 1949.

157. Thiersch, J. B., and Philips, F. S.: Folic acid antagonists in neoplastic disease, Am. J. Med. Sci., 217:575-584, 1949.

158. Thomas, M. I. R., and Cullembine, H.: Nitrogen mustards in Hodgkin's disease, Lancet, 1:899-906, 1947.

159. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Straehlein, D., and Wilson, D. L.: The clinical usefulness of ACTH and cortisone, N.E. Jour. Med., 242:783-793, 824-834, 865-872, 1950.

160. Thorn, G. W., Renold, A. E., Wilson, D. L., Frawley, T. F., Jenkins, D., Garcia-Reyes, J., and Forsham, P. H.: Clinical studies on the activity of orally administered cortisone, N.E. Jour. Med., 245:549-555, 1951.

161. Timmis, G. M.: British Empire Cancer Campaign, Twenty-eighth Annual Report, 1950, p. 58.

162. West, P. M.: Ineffectiveness of chymotrypsin therapy in malignancy, Proc. Soc. Exp. Biol. & Med., 71:252-253, 1949.

163. White, A.: Symposium on steroids in experimental and clinical practice, The Blakiston Co., Philadelphia, 1951.

164. Winternitz, M. C.: "Krebiozen" Committee on Cancer Diagnosis and Therapy, J.A.M.A., 147:1297, Nov. 1951.

165. Wintrobe, M. M., Cartright, G. E., Palmer, J. G., Kubser, W. J., and Samuels, L. T.: Effect of corticotropin and cortisone on the blood in various disorders in man, Arch. Int. Med., 88:310-336, Sept. 1951.

166. Woods, R.: The citrovorum factor, Borden's Review of Nutrition Research, 12: June 1951.

167. Woolley, D. W.: A Study of Antimetabolites, John Wiley & Sons, Inc., New York, 1952.

168. Wright, J. C., Prigot, A., Wright, L. T., and Arous, I.: Further observations on the use of triethylene melamine in neoplastic diseases, A.M.A. Arch. Int. Med., 89:387-404, 1952.

169. Wright, L. T., Wright, J. C., Prigot, A., and Weintraub, S.: Remissions caused by tri-ethylene melamine in certain neoplastic diseases, J. Nat. M. A., 42:343-351, Nov. 1950.

170. Zanes, R. P., Doan, C. A., and Hoster, H. A.: Studies in Hodgkin's syndrome, VII. Nitrogen mustard therapy, J. Lab. & Clin. Med., 33:1002-1018, 1948.

171. Zarafonetis, C. J. D., Andrews, G. A., Meyers, M. C., and Bethell, F. H.: Para-aminobenzoic acid in leukemia, Blood, 3:780-792, 1948.

172. Zarafonetis, C. J. D.: Therapeutic possibilities of para-amino-benzoic acid, Annals Int. Med., 30:1188-1211, 1949.

A Change in VA Report on Patients

VETERANS ADMINISTRATION'S monthly "Statistical Summary of VA Activities" no longer distinguishes between non-service and service connected patients in VA hospitals. Previous summaries indicated that approximately two-thirds of the patients were non-service connected cases, but the current summary gives no indication what percentage of the 98,517 patients are in this category.—*From the A.M.A. Capitol Clinic.*